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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,181	JU ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 74-90 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

3. For purposes of examination, claim 74 has been interpreted as encompassing a method whereby the nucleotide sequence of virtually any DNA can be determined, including intact chromosomes, as well as any number of fragments of any length and of any degree of similarity

to that of the DNA that the artisan truly wishes to sequence. The claimed method has also been construed as encompassing the performance of the claimed method under virtually any condition that would result in any primer extension product, including primer extension products derived from non-target DNA molecules. And the claimed method has been interpreted as encompassing the accurate, reproducible sequencing of any number of DNA sequences in a simultaneous format where the same labels are used for all primer extension products derived from all DNA templates.

4. The claimed method has also been construed as encompassing the use of a system whose surface has been "coated with a compound" where the coating is by covalent or non-covalent binding means.

5. The claimed method has also been construed as encompassing the simultaneous determination of the masses of an infinite number of DNA fragments, irrespective of the template(s) they were derived from, including a heterogeneous mixture comprising premature termination products, full length products of short templates, erroneous incorporation of nucleotides in full length sequences, etc. While Claim 74, step (b), stipulates the generation of fragments of different length, such "fragments" are with respect to the template, which is without bounds. Accordingly, the "fragment" has been construed s being at a minimum, one nucleotide less than the template.

6. Said claim has also been interpreted as encompassing the use of a system where a plurality of wells are in series for each channel, and that the sample is immobilized to the coated surface of the channels by a single passage of the sample through said channels and wells.

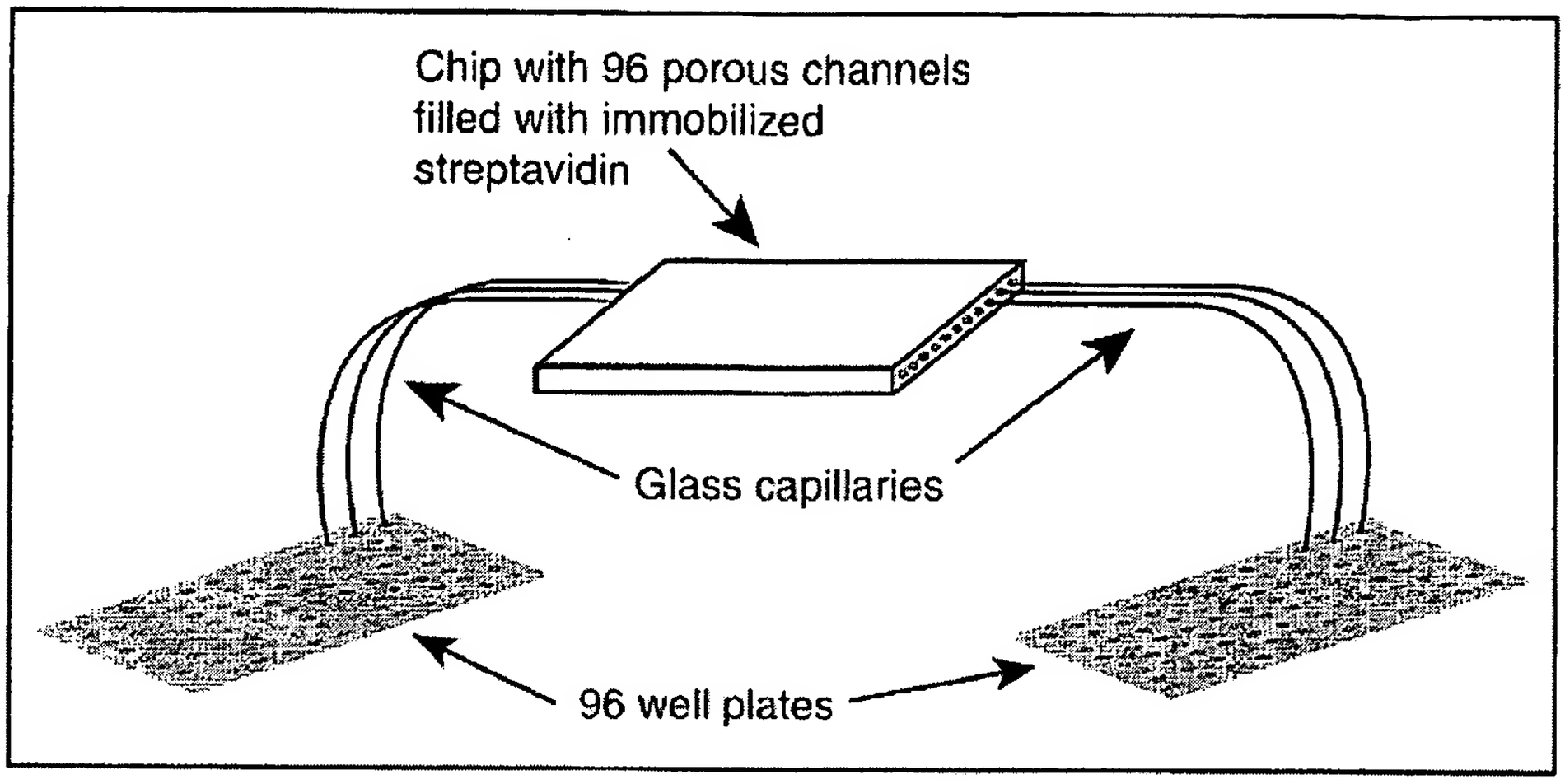
7. The claimed method has been interpreted as encompassing the release of the immobilized DNA sequencing fragments by virtually any means, which include but are not limited to, heating, application of light, application of one or any combination of chemicals, including but not limited to alkaline degradation.

8. Said claim has been interpreted as encompassing determining the difference in molecular weight between different labeled DNA sequencing fragments via mass spectrometry, where the DNA sequencing fragments have not been further manipulated or modified since passage through the channel(s) and well(s). To that end, the claimed method fairly encompasses practicing a method where the samples are not free from alkaline or alkaline-earth salts, or any other contaminant. The instant specification, however, cautions artisans thusly:

> However, in order to obtain accurate measure of the mass of the sequencing DNA fragments, the samples must be free from alkaline and alkaline-earth salts. Samples must be desalted and free from contaminants before the MS analysis.

A review of the specification, including the passages cited by applicant, fails to find an adequate written description of where mass spectrometry is performed on the DNA sequencing fragments where the sample contains any of the above-noted contaminants.

9. As noted above, the claimed method has been interpreted as comprising a plurality of wells connected via a channel. A review of the disclosure reveals a description via Fig. 12, of two 96-well plates that are connected via glass capillary tubes to corresponding single channels in a chip.



It is noted with particularity that the device described lacks any means for applying pressure such that any one, much less 96 different samples could be passed through the coated channels in one direction, much less back-and-forth, thereby permitting/enabling the binding of the DNA sequencing fragments. While the claims have been amended so to recite that there are "wells" located at either end of the glass capillaries, the specification has not been found to support a broader application of where the wells are the ends of the capillaries are anything other than a 96-well plate. For convenience, the relevant portions of page 48 are reproduced below.

> This application discloses a 96-well plate that can be used for sequencing fragment generation with biotinylated terminators as shown in Figure 12. In the example shown, each end of a channel is connected to a single well. However, for other applications, the end of a channel could be connected to a plurality of wells. Pressure is applied to drive the samples through a glass capillary into the channels on the chip. Inside the channels the biotin is captured by the covalently bound streptavidin. After passing through the channel, the sample enters into a clean plate in the other end of the chip. Pressure applied in reverse drives the sample through the channel multiple times and ensures a highly efficient solid phase capture. Water is similarly added to

Accordingly, the broader application of the term "wells" to include wells not of a 96-well plate is deemed to constitute new matter.

10. The claimed method has also been interpreted as encompassing the simultaneous sequencing of multiple DNA sequencing fragments in a common channel. To perform such a maneuver would present situations where multiple signals would be generated at the same time, yet would correspond to the different templates. The use of knowingly different DNA fragments will cause situations where the nucleotide sequence is anything but clearly resolvable. The specification has not been found to provide an adequate written description of how this issue is to be overcome.

11. The claimed method fairly encompasses the use of mass spectrometry in the analysis of the DNA fragments. The use of lasers in performing mass spectrometry is recognized in the art

as causing significant problems in sequencing. In support of this position attention is directed to US Patent Application Publication 2002016842A1 teaches at paragraph 13:

> A problem encountered with MALDI of simplex DNA is breakage. Initial trials with short homogenous simplexes revealed severe fragmentation problems ("Matrix-assisted laser-desorption mass spectrometry of DNA using an infrared free-electron laser," Haugland, R. F. et al.; Proc. SPIE-Int. Soc. Opt. Eng., 1854 (FEL), 1993). Two distinct molecules of lower mass are split off by a break in the deoxyribose-phosphodiester backbone of single stranded DNA. Even for a homogenous population of single stranded DNAs, the resultant fragments have a broad range of lower masses. For projected heterogeneous single stranded Pop as inputs for sequencing, lower mass members will be within the fragmentation background and thus harder to recognize.

As presently worded, the claimed method requires the application of conditions which cause cleavage of the nucleic acid molecule; see claim 81 where the linker is used, and claim 82 where cleavage means include "physical means, a chemical means, a physical chemical means, heat, and light." Clearly, these methodologies can cleave more than the linker, e.g., the sequencing fragment at other places. The specification of the subject application has not been found to provide an adequate written description as to how art-recognized issues are to be overcome.

12. In accordance with the claimed method, the individually labeled sequencing fragments that are recognizable on the basis of the mass of the label attached to the terminating nucleotide.[1] Independent claim 74, however, seemingly contradicts requirements of steps (a) and (b) wherein step (f) the label is not necessarily a biotinylated nucleotide, but could be some form of a linker.

13. As set forth in claim 81 (as well as dependent claims 82-83), for example, the sequencing fragment is separated from this mass-identifiable label by "cleaving the linker." Seemingly, by

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[1] Claim 74, step (a), last clause reads "wherein each of the four different labeled dideoxynucleotides has a molecular weight which can be distinguished from the molecular weight of the other three labeled dideoxynucleotides using mass spectrometry." Claim 1, step (b) states further that "the chemical moiety [the label] is attached via the linker to the 3' end of the DNA sequencing fragment."

cleaving the DNA sequencing fragment from is requisite label, one is not able to effectively determine the mass of the terminating nucleotide, and therewith, its identity, and the identity of the sequence of nucleotide of which the target sequence is comprised. The specification has not been found to set forth a full, clear, and concise description of how such seeming contradictory steps can be performed.

14. In view of the breadth of the claims, the limited written description provided, and the apparent non-functionality of the claims, the specification has not been found to provide an adequate written description of the invention. Similarly, the specification has not been found to reasonably suggest that applicant was in possession of the invention at the time of filing. Therefore, and in the absence of convincing evidence to the contrary, claims 74-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

15. At page 16 of the response received 26 September 2005, applicant's representative asserts that it is improper for the Office to read limitations into the claims, citing no recitation of the claims encompassing the sequencing of an infinite number of sequences, or of the location of wells. This argument has been fully considered and has not been found persuasive. As set forth at MPEP 2106:

> (CCPA 1969). See also *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.").

In the present case, the aspect of the claim reciting "a method for sequencing a DNA" has been interpreted as encompassing any DNA, where "any" includes any length, composition, and number. It is noted with particularity that the claims do not recite that "only one" DNA sequence is being determined, much less stipulate that the one DNA sequence/template is isolated from all other DNA molecules.

16. At page 17 (and at page 18) of the response argument is provided that "one skilled in the art reading the specification and reviewing the example referred to, and explicitly shown, could see that applicant was clearly in possession of the claimed invention." This argument has been fully considered and has not been found persuasive. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

17. Agreement is reached in that the inclusion of a step whereby unincorporated materials are removed prior to analysis does move the claim forward, other issues, as developed above, still remain.

18. For the above reasons, and in the absence of convincing evidence to the contrary, claims 74-90 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

19. Claims 74-90 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737,

> 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

20. As presented above, the specification has not been found to provide an adequate written description of the invention to where the specification does not reasonably suggest that applicant did not possess the entire invention at the time of filing. It is well settled that one cannot enable that which they do not yet possess.

21. Further, the records clearly shows that the claimed method fairly encompasses embodiments where art-recognized issues of enablement would be encountered, yet the specification is effectively silent as to how they are to be overcome sans the skilled artisan resort to undue experimentation.

22. Therefore, and in the absence of convincing evidence to the contrary, claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Response to arguments

23. At page 19, bridging to page 20 of the response argument is presented that "applicants note that the mass resolution of the claimed method is sufficient to distinguish the different fragments by mass spectrometry," directing attention to application of MALDI-TOF and examples.

24. The above argument has been fully considered and has not been found persuasive as the specification does not set forth a reproducible procedure where a) a mixture of divergent nucleic acids can all be sequenced in the same reaction; b) nucleic acid segments, cleaved from their

label, are subjected to mass spec and have their terminating nucleotide correctly identified when the method stipulates that such identification is achieved by the presence of the label; and c) the correct nucleotide sequence is determined when one employs cleavage means selected from the group consisting of physical means, chemical means, physical chemical means, heat, and light.

25. The specification does not set forth the essential starting materials and reaction conditions under which the full scope of the claimed invention is enabled. Indeed, it is not enough that one small part of a claim's scope be enabled; rather, applicant's disclosure must enable the full scope of that encompassed by the claims. For the above reasons, and in the absence of convincing evidence to the contrary, claims 74-90 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

26. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

27. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

29. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

30. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
01 December 2005